The Egyptian Journal of Otolaryngology

ORIGINAL ARTICLE Open Access

Co-occurrence of delayed language development and autism spectrum disorder in children with metabolic disorders

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Abstract

Background Children with various metabolic disorders are considered a high-risk group for different developmental delays. Delayed language development (DLD) and autism spectrum disorder (ASD) have a common incidence in children with metabolic disorders which negatively impact their social and academic life. So, early assessment of this high-risk group for the presence of DLD and/or ASD is of great significance and providing better prognosis through starting therapy as early as possible.

Aim of the work It aims to detect the presence of DLD and ASD among children with metabolic disorders.

Methods This is an analytical (observational) cross-sectional study. The subjects of this study comprised a convenient sample of 100 children diagnosed as having different metabolic disorders with age range between 24 and 48 months. The Modified Preschool Language Scale, Fourth Edition–Arabic version and the Childhood Autism Rating Scale were applied for all children, to detect the presence of DLD and ASD.

Results Assessment of 100 children with unequal distribution of 13 types of metabolic disorders found that 86% of cases had DLD and 16% had ASD. Regarding different metabolic disorders, we found both DLD and ASD in nine types and only DLD in four types of metabolic disorders.

Conclusion Children with metabolic disorders are at a high risk for DLD and ASD. Early detection of these cases provides early intervention and better outcome.

Keywords Autism spectrum disorder, Metabolic disorders, Delayed language development, Modified preschool language scale

Background

There are hundreds of inherited metabolic disorders (MD), caused by different genetic defects. These disorders are predominantly affecting the pediatric population and cause multiple systemic physiological abnormalities and neurological deficits [1].

As the central nervous system is frequently involved, children with MD often present with disorders affecting motor and cognitive systems. Many children with MD do present with epilepsy and psychomotor retardation. Consequently, children born with various types of MD may present with an array of communication impairments

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ranging from mild developmental delay to severe intellectual disability and social-behavioral disorders such as autism spectrum disorder (ASD) [2].

Symptoms of ASD can be a seen in a lot of MD and rarely in isolation, since MD are sometimes treatable. Given the enormous etiological factors of autistic symptoms, including genetic and metabolic causes, team diagnosis of these children should include efficient genetic and metabolic studies chosen on the basis of leading symptoms and associated clinical signs [2]. A metabolic disorder occurs when abnormal chemical reactions in the body disrupt this process. When this happens, it leads to failure of elimination of toxic waste products or failure in producing essential products. There are different groups of disorders. Some affect the breakdown of amino acids, carbohydrates, or lipids. Another group, mitochondrial diseases, affects the parts of the cells that produce the energy. The cause of this disturbance is inheritance of two defective gene copies which cannot produce enough effective enzymes. So, it is called genetic metabolic disorder/inherited metabolic disorders [1]. There are hundreds of inherited metabolic disorders, caused by different genetic defects.

The researchers have identified four main mechanisms highly contributing to formation of metabolic biomarkers associated with communication deficits, which are as follows: oxidative stress [3], mitochondrial dysfunction [4], deficiency of certain nutrients [5], and altered immune function [6].

The latest update of *Diagnostic and Statistical Manual* (DSM-V) has enclosed ASD symptoms in two main criteria which are persistent deficits in social communication and social interaction and restricted, repetitive patterns of behavior, interests, or activities. Also, it described the presence of another medical or genetic condition as a diagnostic specifier [7].

The prevalence of ASD has a worldwide increase to 1 case of ASD in every 100 children [8]. ASD is a mysterious disorder as no definite cause can be claimed for it, but recent research and clinical studies in ASD have implicated physiological and metabolic systems abnormalities that go beyond organ-specific dysfunction [9]. Although ASD symptoms appear in the early 2nd year of life, most of cases are discovered after the 3rd year. So, the early language assessment of children with high risk for communication disorders is mandatory. Since the 1st 3 years represent the golden age for the language acquisition, so early intervention with language, cognitive, and behavior therapy provides better prognosis [10].

The aim of this work is to detect the presence of delayed language development (DLD) and ASD among children with metabolic disorders using the Modified Preschool Language Scale, Fourth Edition–Arabic version (PLS-4) and the Childhood Autism Rating Scale (CARS) respectively as diagnostic tools.

Methods

Type of study

It is an analytical (observational) cross-section study.

Patients

This study was applied on 100 children diagnosed as having metabolic disorders in the Pediatric Neurology Clinic in El-Demerdash Hospital.

Inclusion criteria

- The child is already diagnosed with a specific metabolic disorder for more than 6 months.
- The child age is between 24 and 48 months.

Exclusion criteria

- The child has hearing impairment.
- The child has blindness.

Clinical tools

For assessment of children, the following selected assessment steps, extracted from the language assessment protocol that is structured and used at the Unit of Phoniatrics Ain Shams University, was used:

1. *History taking* (taking in consideration the duration of the treatment and the compliance of the patient)
2. *Examination is as follows:*
    a. Ear, nose, and throat examination
    b. Neurological and psychiatric examination
    c. General examination
3. *Mental age*: Using Stanford-Binet Intelligence Scale [11, 12].
4. *Language assessment*: By the Modified Preschool Language Scale, Fourth Edition–Arabic version (PLS-4) [12, 13]. This test determines the receptive, expressive, and total language age of the child, giving a standard score. So, any child obtained standard score less than the normal range is considered to have DLD.
5. *Childhood Autism Rating Scale (CARS)*: It is a behavior observation scale in which a psychotherapist rates the child's behavior on each of 15 dimensions or symptoms [14, 15]. It is useful as a measure of degree

of severity of autism: not autism (score < 30), mild-to-moderate autism (score 30–36), or severe autism (score > 36) [13].

Method

All children with MD coming for follow-up in the Pediatric Neurology Clinic, meeting our inclusion criteria, and not within the exclusion criteria were included in the study. The collection of data took 3-month duration.

Children scoring below the normal standard score for PLS-4 (which is 77.5) were considered as having DLD.

Children scoring 30 or more in CARS were considered as suffering from ASD.

Ethical considerations

Parental informed consent was taken for all subjects.

- *Sampling method*: Purposive sampling according to the inclusion criteria
- *Sample size*: By using PAS 11 program for sample size calculation, setting confidence level at 95% and margin of error ± 0.10, and by reviewing previous study results [2], it shows that the rate of the delayed language development was 33.5%, and the rate of autism spectrum disorder was 2.4% among children with inborn errors of metabolism; based on that, a sample size of at least *100 patients with metabolic disorders* will be sufficient to achieve study objective.
- *Statistical analysis*: Data was collected, revised, coded, and entered to the Statistical Package for Social Science (SPSS) version 20, and the following was done:

Qualitative data were presented as number and percentages, while quantitative data were presented as mean, standard deviations, and ranges.

The comparison between two groups with qualitative data was done by using *chi-square test*, and/or *Fisher exact test* was used instead of chi-square test when the expected count in any cell was found less than 5.

The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the *p*-value was considered ± significant as the following:

- $p > 0.05$: Nonsignificant
- $p < 0.05$: Significant
- $p < 0.01$: Highly significant

Results

This study was conducted on 100 Egyptian children diagnosed with a known metabolic disorder in the pediatric neurology clinic.

1. The 100 studied cases were unequally distributed among 13 metabolic disorders. The most frequent disorders were the mitochondrial disorder (17%), phenylketonuria (PKU) (11%), and gluten defect (10%), respectively. The less frequent disorders are neural ceroid lipofuscinosis and neurometabolic disorder 3% for each one as shown in Fig. 1.
2. The total number of DLD cases in MD was 86 cases (86%). Regarding the distribution of language development in each type of studied metabolic disorders, the group of glucose-6-phosphate dehydrogenase (G6PD) deficiency has the highest number of normal language development (NLD), 5 cases (55%), while the group of the mitochondrial disorder has the highest number of the delayed language development (DLD), 16 cases (94%). Moreover, 100% of the cases

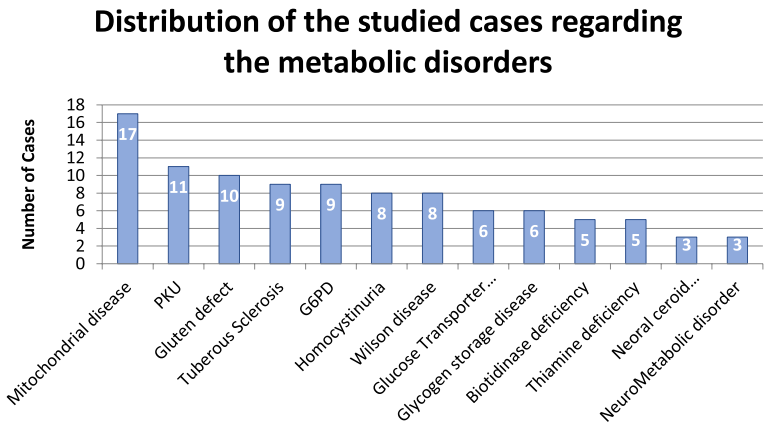

Fig. 1 Metabolic disorders distribution in the study group ($n = 100$)

of the following groups (phenylketonuria with 11 cases, homocystinuria with 8 cases, biotinidase deficiency with 5 cases, tuberous sclerosis with 9 cases, Wilson disease with 8 cases, thiamine deficiency with 5 cases, and neurometabolic disorder with 3 cases) show delayed language development as shown in Fig. 2.

3. The total number of ASD cases in all studied MD was 16 cases (16%). Concerning the distribution of ASD cases in each metabolic disorder, the mitochondrial disorder group has the highest number of ASD cases, 4 cases (23%). Moreover, 100% of glucose transporter defect (6 cases), G6PD (9 cases), neural ceroid lipofuscinosis (3 cases), and glycogen storage disease (6 cases) children have not showed any ASD cases as shown in Fig. 3.
4. There is nonsignificant relation between the sex whether male or female and presence of DLD and ASD cases as p-value > 0.05 as shown in Table 1.
5. We classified our cases according to the compliance of treatment for the MD into two groups: 1st group with cases who were regular on the treatment intake for more than 3 months (compliant) and 2nd group which includes those who did not take the treatment

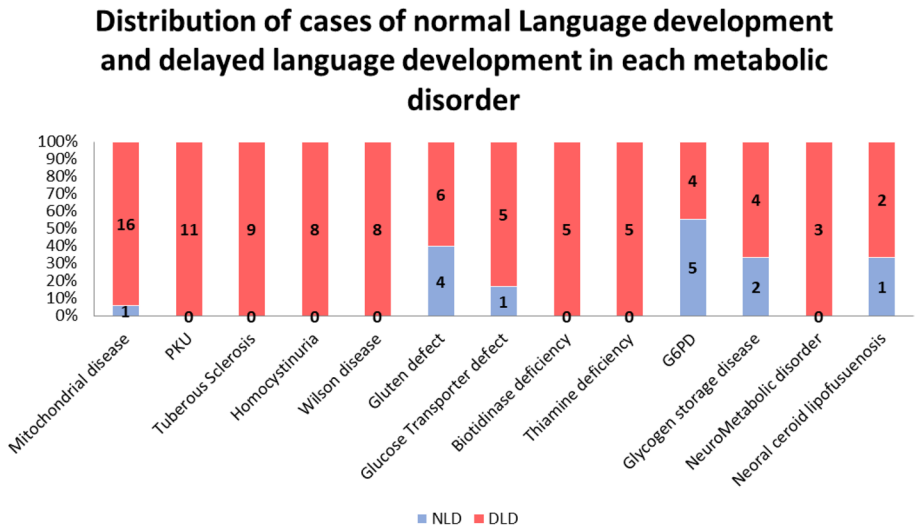

Fig. 2 The distribution of cases of normal language development and delayed language development in each metabolic disorder

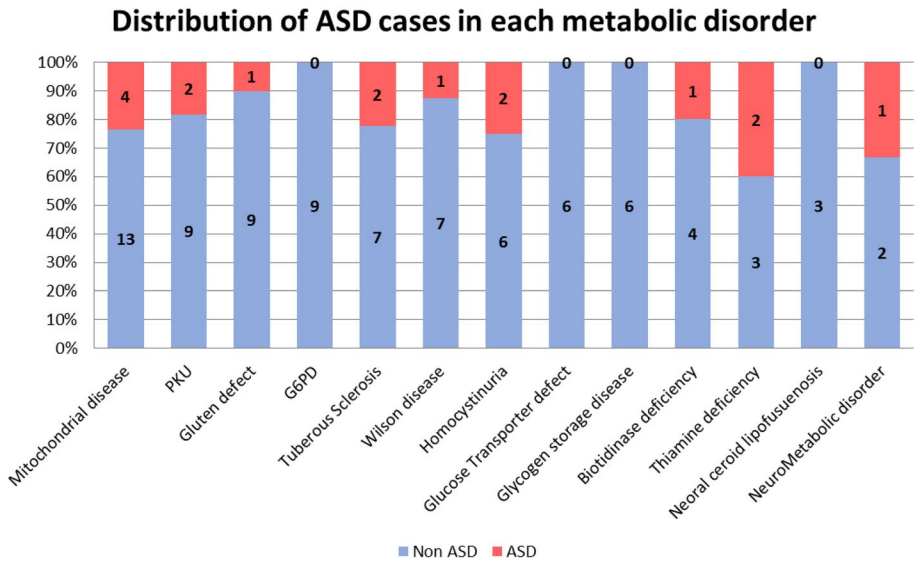

Fig. 3 The distribution of the ASD cases in each metabolic disorder

Table 1 The relation between the effect of gender on the presence of delayed language development and autism spectrum disorder

		Sex		Test of sig	
		Male	Female		
		N (%)	*N* (%)	*p*-value	Sig
Language development	NLD	10 (13.89%)	4 (14.29%)	1(F)	NS
	DLD	62 (86.11%)	24 (85.71%)		
Autism spectrum disorder	No	60 (83.33%)	24 (85.71%)	1(F)	NS
	Yes	12 (16.67%)	4 (14.29%)		

NLD normal language development. *F* Fisher exact test. *NS* non-significant

Table 2 The relation between the treatment compliance to the language development, CARS results, and autism spectrum disorder

		Treatment compliance		Test of sig	
		Compliant	Non-compliant		
		N (%)	*N* (%)	*p*-value	Sig
Language development	NLD	12 (19.35%)	2 (5.26%)	0.049(C)	S
	DLD	50 (80.65%)	36 (94.74%)		
CARS	No	40 (88.89%)	22 (66.67%)	0.016(F)	S
	Mild to moderate	5 (11.11%)	11(33.33%)		
	Severe	0 (0%)	(0%)		
Autism	No	57 (91.94%)	27 (71.05%)	0.006(C)	S
	Yes	5 (8.06%)	11 (28.95%)		

NLD normal language development. *S* significant. *F* Fisher exact test. *C* chi-square

regularly and who took the treatment for less than 3 months (non-compliant). There was a significant relation between the noncompliance to the medical treatment of the MD and the presence of DLD, CARS results, and the presence of ASD. Also, there was a significant relation between the more compliance and normal language development, normal score in CARS, and no autism. *p*-value was 0.049, 0.016, and 0.006, respectively, as shown in Table 2.

Discussion

Metabolic disorders (MD) are a group of rare single-gene defects that result from the abnormalities in either the synthesis or catabolism of proteins, carbohydrates, or fats by defective enzymes or transport proteins, leading to a block of the metabolic pathway resulting in impairment of most of brain functions and development.

MD involves brain damage which is more likely to result in a range of communication disorders in young children.

The current research aims to study the presence of DLD and ASD in children with MD. It was done on 100 cases (age between 24 and 48 months) with confirmed diagnosis with 13 different MD.

Regarding the presence of delayed language development (DLD), our study revealed that 86% of the studied cases had DLD and 16% of the studied MD cases had ASD.

A study made by Tiwari et al. investigated the communication disorders with the metabolic disorder. It showed that delayed language development was seen in almost 50% of the children with a diagnosis of MD, while only 2.4% of its MD studied cases had ASD. The different results may be due to different age groups as they worked on an older sample (up to 19 years old), and also, they used different language assessment tools [2].

Other investigators have recommended that care must be taken in considering screening for MD in ASD patients [12], and they have appropriately cautioned that correlation of behavioral similarities between ASD and those observed in genetically determined syndromes (e.g., Fragile X, Angelman) should be carefully interpreted.

Regarding the relation between the type of the metabolic disorder and the presence of DLD and ASD in the studied cases (Figs. 2 and 3), both were included together in nine metabolic disorders, while there were four types with no ASD cases, only DLD. We will discuss each type from the highest number of ASD cases to the lowest regarding the risk for ASD, the final diagnosis, the language development, and the causative relation with ASD.

- *Mitochondrial disorder (n = 17)*: It had 4 ASD cases (23.5%) and 13 non-ASD (76.47%). According to the normal standard scores of PLS-4, 1 case (5.9%) had normal language development (NLD), while 16 cases (94.1%) had delayed language development (DLD). Rossignol and Frye [4, 5] concluded that almost one-third (30%) of autistic children have documented elevations in the biomarkers of mitochondrial dysfunction, which is a near ratio to our study.
- *Phenylketonuria (PKU) (n = 11)*: It had 2 ASD cases (18.2%) and 9 non-ASD cases (81.8%). A study done in Sudan by Khemir et al. [16] found that 15 children (79%) in their study had autism, while 5.7% of late-diagnosed PKU children had ASD. The variation in the percentages between studies may be due to the difference in PKU populations, whether early-treated, late-treated, or mixed and different used

modalities in ASD diagnosis. While in our study, no cases had NLD, and 11 cases (100%) had DLD.

Homocystinuria (HCY) (n=8): It had 2 ASD cases (25%) and 6 non-ASD cases (75%). It is comparable with the results of a recent studies done by de la Bâtie et al. [17] who found only 10.5% of HCY cases had ASD. A study by Czaplińska et. al. [18] suggested a very important relationship between high levels of homocysteine and deficiencies of vitamins B: B6, B12, and folic acid which is vital for the proper functioning of autistic children. The high level of serum and urinary homocysteine is associated with pathophysiology of autism spectrum disorders and may serve as a diagnostic tool for the detection of nutrient deficiencies in the case of autistic children. However, it should be very carefully considered whether abnormal levels of homocysteine are the result of nutritional deficiencies, or they result from genetic disorder. Almuqbil et al. [19] documented that those non-ASD cases are also at a great risk for other developmental and psychiatric disorders other than ASD. No cases had NLD, and 8 cases (100%) had DLD.

- *Tuberous sclerosis complex (TSC)*: It had 2 ASD cases (22.2%) and 7 non-ASD cases (77.8%). It is less than the ratio obtained by Sundberg and Sahin [20] who found 50% of TSC cases had ASD. It may be due to the latter one focused in his study on TSC cases only unlike our study which included it through different metabolic disorders. No cases had NLD, and 8 cases (100%) had DLD. Recent studies concluded that the abnormal cerebellar development, due to a variety of causes, including abnormal regional expression of *TSC1*, *TSC2 genes*, and related gene networks, may contribute to cognitive and neuropsychiatric disorders such as ASD [21].
- *Thiamine deficiency*: It had 2 ASD cases (40%) and 3 non-ASD cases (60%). The relation between thiamine deficiency and ASD had a lot of debate, and some research stated that inadequate intake of thiamine had been identified as a risk factor for ASD. It is supported by a pilot study that was made over 10 ASD cases; the ratio of thiamine deficiency was 3 (30%), and after the treatment by the deficient vitamin for all the 10 cases, 8 of them showed improvement in the behavioral manifestations [22]. On the other side, another research found no significant correlation of the plasma and urine thiamine concentration in a case–control study between ASD and non-ASD groups [23]. While in this study, no cases had NLD, and 5 cases (100%) had DLD.
- *Biotinidase deficiency (BTD)*: It had 1 (20%) ASD cases and 4 (80%) non-ASD cases. No cases had NLD, and 5 cases (100%) had DLD. The results of our study are near to the results of a Scottish study done by Ogundele [24] which detected the abnormal developmental comorbidities with BTD. A total of 49.4% of BTD cases had social communication concerns and ASD. Nearly 63.4% of cases had global developmental delay and delayed language development. ASD ratio in our study is less than the Scottish study due to higher ASD prevalence in Scotland which reached around 700,000 people who may be autistic indicating that 1.1% of the population in the UK may be on the autism spectrum.

Wilson disease: It had 1 case (12.5%) ASD case and 7 (87.5%) non-ASD cases. It usually presents later after 4–5 years old until the excessive copper deposition exists. Chinese study proved an association between serum levels of copper (Cu) and ASD, and they considered elevated Cu ratio as a biomarker of ASD [25]. No cases had NLD, and 8 cases (100%) had DLD.

- *Gluten defect*: It had 1 case (10%) ASD case and 9 (90%) non-ASD cases. There were 4 cases (40%) which had NLD, and 6 cases (60%) had DLD. Although some researchers proved ASD children have gastrointestinal problems including a "leaky gut" leading to increase of the circulatory peptide fragments caused by the breakdown of gluten "gliadine morphines," respectively, these products act centrally as endogenous opioids which may interfere with normal behavior in children, although there is no sufficient evidence to advise the gluten-free diet for improving the symptoms of ASD in children [26].
- *Neurometabolic disorders*: It had 1 (33.3%) ASD case and 2 (66.7%) non-ASD cases. No cases had NLD, and 3 cases (100%) had DLD. It goes with a significant correlation between the ASD and abnormal plasma levels of metabolites in methionine transmethylation and transsulfuration pathways, and common polymorphic variants known to modulate these metabolic pathways were evaluated also in 360 autistic children and 205 controls. The metabolic results indicated that plasma methionine and the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH), an indicator of methylation capacity, were significantly decreased in the autistic children relative to age-matched controls. In addition, plasma levels of cysteine, glutathione, and the ratio of reduced to oxidized glutathione, an indication of antioxidant capacity and redox homeostasis, were significantly decreased in ASD cases [27].

As we mentioned before, there were four types of metabolic disorders in our study that did not show any ASD cases which are as follows:

- *Glucose transporter deficiency (GLUT)*: It had no ASD cases out of six cases. It is similar to previous studies which stated that both ASD and GLUT are overlapping as GLUT is represented by mixed movements, e.g., chorea, ataxia, dystonia, and myoclonus but not typical stereotyped movements of ASD [28]. No cases had NLD, and 3 cases (100%) had DLD. It is going with the previous studies result who stated that GLUT cases have varying degrees of speech, and language impairment especially dysarthria, dysfluency, receptive and expressive language skills disturbance, and sometimes expressive language skills are disproportionately affected [29].
- *Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency)*: It had no ASD cases out of nine cases. It is similar with other studies which found only 2 ASD cases out of 49 G6PD cases who had severe language delay with mental retardation, and 1 also had a seizure disorder. The study assumed two relative causes which are the development of kernicterus resulting from hyperbilirubinemia, or it may be sporadic comorbidity [30]. Five cases (55.5%) had NLD, and 4 cases (44.4%) had DLD.
- *Glycogen storage disease*: It had no ASD cases out of six cases. Özaslan et.al. [31] documented that there is no relation between GSD and autism. GSD is mainly presented in the first year of life with severe fasting hypoglycemia, hepatomegaly, failure to thrive, growth retardation, and developmental delay [32]. It is comparable with our study as we have 2 cases (33.3%) which had NLD and 4 cases (66.7%) which had DLD.
- *Neoral ceroid lipofuscinosis*: It had no ASD cases out of three cases. There was 1 case (33.3%) which had NLD, and 2 cases (66.7%) had DLD. Our study's result is expected as it is a group of conditions that affect the nervous system. Signs and symptoms vary widely between the forms but generally include a combination of dementia, vision loss, and epilepsy. Intellectual disability is present in 80–99% of these patients with subsequent language delay as a result [33].

Lastly, in our study, we compared the relation between the compliance to the treatment of MD and the ASD frequency and language development as shown in Table 2. By comparing the NLD and DLD, the compliance of treatment has p-value (0.049) which is significant.

By comparing the results of CARS test (no autism, mild-to-moderate and severe), the treatment compliance has a p-value (0.016) which is significant.

By comparing ASD and non-ASD cases regarding the treatment, compliance has p-value (0.006) which is significant.

ASD, considered as chronic illnesses, noncompliance in management can lead to unmet treatment expectations. In developed countries, approximately 50% of the patients with chronic illnesses follow treatment. In developing countries, poor compliance threatens to render any efforts to manage chronic conditions ineffective [34]. In our study, the significance of the treatment compliance and its effect on severity of the case is obvious.

Limitations of the present study is the small number of studied cases, especially in neoral ceroid and neurometabolic disorder because of the limited number of cases with confirmed diagnosis before 48 months (the age of studied case) of these two disorders. Also, some diagnostic tools for MD are very expensive and unavailable, so we could not include some cases with doubtful diagnosis.

Conclusion

Metabolic disorders especially mitochondrial disorders are highly comorbid with ASD and DLD, but the exact pathophysiology is still not clear. Children with metabolic disorders are at a high risk. So, screening of ASD and DLD is mandatory for this group. ASD as well as DLD affects the long-life quality for the case and his/her family. So, early diagnosis provides early intervention and better outcome.

Recommendation

More continuous research is important to prove that the controlled treatment of the metabolic disorder is improving the accompanied neurodevelopmental delays, e.g., DLD and ASD symptoms, or even lessen its incidence. Also, we recommend referring high-risk children coming to pediatric clinics to phoniatricians for thorough examination and language assessment to ensure early detection and management of cases aiming to better prognosis.

Acknowledgements

Not applicable

Authors' contributions

ASA formulated the idea and aim and conducted the research process. LA performed the writing and editing. MOS designed the work. HHG provided the study material and interpretation of data. DAE acquired the data, applied the statistical techniques, and writing the original draft.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Parental informed consent was taken for all subjects and the study protocol has been approved by the Ain Shams Institute's Ethical Committee of Human Research.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 30 November 2023 Accepted: 16 February 2024
Published online: 12 March 2024

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